

Patent claims

1. Process for the fast and efficient discovery and preparation of new compounds, characterised by
 - (1) selection of M different starting materials suitable for multicomponent reactions (MCRs),
 - (2) reaction of each starting material with ~~another of or with~~ every possible combination of **from 2** to M-1 other starting materials selected according to (1),
 - (3) analysis of the products,
 - (4) evaluation of the products and selection of at least one product,
 - (5) determination of the starting materials that have led to the product(s) selected in (4), and
 - (6) provision of at least one variant of at least one of the starting materials that have been determined in (5),
 - (7) reaction of the starting materials provided in (6) if appropriate with the remaining starting materials determined in (5) in the context of an MCR,
 - (8) repetition of steps (4) to (7) until at least one product having the desired property or properties is found, and
 - (9) optionally isolation and characterisation of the product.
2. Process according to claim 1, characterised in that $M \leq 40$.

3. Process according to either one of the preceding claims, characterised in that in (1) and/or in (6) reaction conditions suitable for MCRs are also selected.
- ~~4. Process according to any one of the preceding claims, characterised in that in (2) each starting material is reacted with every possible combination of from 2 to M-1 other starting materials selected according to (1).~~
5. Process according to any one of the preceding claims, characterised in that the analysis according to (3) is a biological and/or pharmacological and/or physico-chemical analysis.
6. Process according to any one of the preceding claims, characterised in that in (4) all products are evaluated.
7. Process according to any one of the preceding claims, characterised in that in (4) the reaction conditions for preparing the products are also evaluated.
8. Process according to any one of the preceding claims, characterised in that the reaction according to (7) of the starting materials provided in (6) is if appropriate carried out with the remaining starting materials determined in (5) with the exception of the starting material(s) of which variants were provided in (6).
9. Process according to any one of the preceding claims, characterised in that for each reaction according to (7) only one molecule is selected per starting material type.
10. Process according to any one of the preceding claims, wherein the starting materials have functional groups

customary in organic chemistry, such as -NC, -CO-, -CS-, -CN, -OCN, -NCO, -NO, -NO₂, -ONO₂, -CHO, -COOR, -COSR, -CSSR, -COCOOR, -SCN, -NCS, -halo, -N₃, -NNNR, -OR, -SR, -OCOOR, -SCOOR, -NRCOOR', -OCSOR, -SCSOR, -NRCSOR', -OCSSR, -SCSSR, -NRCSSR', -OCONR'R, -SCONR'R, -NRCONR'R'', -NRR', -NRR'NR'R'', -CNNRR', -CNNRR'HX, -NRCONR'R'', -NRCSSNR'R'', -RCOCR'R'', -RCSCR'R'', -COCRR'halo, -RCNR'CR'', wherein R, R' and R'' are H or alkyl, aryl, aralkyl, hetaryl or hetarylalkyl.

11. Process according to claim 10, wherein the functional groups are epoxy groups or carbenes or the unsaturated vinylogous variants alkene, alkyne, aryl groups or corresponding mono-, di-, tri-, tetra-, penta- or hexa-carbonyl variants of those groups.
12. Process according to claim 10 or 11, wherein two, three, four or more functional groups are present simultaneously in one or more starting materials in suitable combination.
13. Process according to claim 10, wherein the starting materials are starting materials especially suitable for multicomponent reactions, such as alpha-haloketones, esters, carboxylic acids, thiocarboxylic acids, aldehydes, amines, ketones, isonitriles, nitriles, alpha-keto acids, alpha-keto esters, and derivatives and alpha-beta unsaturated variants thereof, and also combinations thereof.
14. Process according to claim 4, wherein the starting materials have corresponding mono-, di-, tri-, tetra-, penta- or hexa-carbonyl variants of the functional groups.
15. Process according to any one of claims 10 to 14, wherein

some of the functional groups of the starting materials are provided with protecting groups customary in organic chemistry.

16. Process according to any one of the preceding claims, wherein the selected starting materials are encoded in a form accessible to an algorithm, the selected starting materials being assigned, either randomly or systematically, unambiguous binary, decimal or alphanumeric codings.
17. Process according to any one of the preceding claims, wherein a starting material type of a specific chemical class is assigned a characteristic coding for that chemical class.
18. Process according to any one of the preceding claims, wherein in the first cycle of the process only those starting materials which belong to different chemical classes are selected.
19. Process according to any one of the preceding claims, wherein the starting materials are selected in accordance with an algorithm.
20. Process according to any one of the preceding claims, wherein multicomponent combinations MCC(K) selected in accordance with an algorithm of different selected starting materials are reacted simultaneously or in a sequential order under conditions customary in organic chemistry.
21. Process according to any one of the preceding claims, wherein each selected combination of starting materials is reacted in a physically separate, optionally encoded

reaction vessel.

22. Process according to any one of the preceding claims, wherein at least some of the resulting reaction products are, in a subsequent step, chemically modified, worked-up or prepared for step (3) in a suitable manner.
23. Process according to any one of the preceding claims, wherein additional auxiliaries or catalysts, such as, for example, Lewis acids, such as boron trifluoride etherate, zinc chloride, ytterbium triflate, iron chloride, other acids, such as, for example, hydrochloric acid, para-toluenesulfonic acid, acetic acid, or bases, such as, for example, potassium carbonate, triethylamine, caesium carbonate, or water-removing agents, such as molecular sieves or orthoesters, are used.
24. Process according to claim 22 or 23, wherein the chemical modification is the removal of chemical protecting groups, for example by trifluoroacetic acid, or the hydrogenation of the products by means of hydrogen, optionally with the addition of a hydrogenation catalyst, such as palladium on carbon, platinum oxide, palladium acetate, or by oxidation of the products with oxygen or some other oxidising agent, such as, for example, bromine, hydrogen peroxide, tert-butyl peroxide or a suitable metal salt, such as cobalt chloride, or a suitable metal complex, such as, for example, iron hexacyanoferrate or chromium tetraphenylporphyrinate, or by irradiation with light of wavelength 200-600 nm, or the reaction products are treated with at least one enzyme, such as, for example, oxidoreductases, ligases, peptidases, lipases or isomerases.
25. Process according to claim 22, wherein the working-up of

the products is carried out in a manner known *per se* by chromatography, for example over silica gel or RP-18 silica gel, or solid phase extraction or the removal of unreacted starting materials by binding to a suitable solid carrier, such as, for example, ion exchanger resins or chemically modified solid phase resins, or by selective binding of the products to a suitable solid carrier.

26. Process according to claim 20 or 23, wherein the reaction conditions and auxiliaries used or catalysts are assigned, either randomly or systematically, unambiguous binary, decimal or alphanumeric codings.
27. Process according to claim 21, wherein the allocation of the various encoded combinations to the reaction vessels is encoded, either randomly or systemically, in binary, decimal or alphanumeric form.
28. Process according to claim 22 or 25, wherein the working-up of the products is assigned, either randomly or systematically, binary, decimal or alphanumeric codings.
29. Process according to any one of the preceding claims, wherein both the starting materials, reaction conditions, modifications, working-up procedures or procedures in preparation for testing that are used and the reaction vessels are encoded.
30. Process according to any one of the preceding claims, where the MCR is a Passerini or Ugi multicomponent reaction with up to 20 components, preferably with 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 components.
31. Process according to any one of the preceding claims,

wherein the products are investigated in a biological and/or pharmacological test for their pharmacological or biological activity, effectiveness, side effects and/or selectivity and/or in a further test procedure for their physico-chemical properties.

32. Process according to claim 31, wherein the dependency of the measurement results upon the concentration of the starting materials used in process step two is ascertained, the concentration lying especially in a range of from 0.5 to 0.000001 mol/l.
33. Process according to claim 32, wherein the concentration lies in a range of from 100 to 0.01 mol/l.
34. Process according to any one of claims 31 to 33, wherein the test for ascertaining the biological or pharmacological activity, effectiveness, side effects or selectivity is carried out with isolated proteins, receptors, enzymes, or mixtures thereof, cells, cell lysates, complex cell systems, with organs or parts thereof or a plurality of organs or with whole organisms or membranes and as appropriate using adjuvants, substrates or detection aids necessary for the test.
35. Process according to any one of claims 31 to 33, wherein the test procedures for the physico-chemical properties of the products include the measurement of the lipophilicity by means of the octanol-water distribution coefficient, the solubility in water, the non-specific protein binding to, for example, bovine serum albumin, the binding to the proteins of human serum plasma and/or the chemical stability in Krebs buffer.

36. Process according to any one of the preceding claims, wherein the test results obtained are related to the codings of the individual reaction products.
37. Process according to claim 36, wherein the test results are stored in a form accessible to an algorithm, for example in a computer data file or a computer data bank.
38. Process according to any one of the preceding claims, wherein the list of the codings and the associated test results fulfil all the prerequisites necessary for further optimisation.
39. Process according to any one of the preceding claims, wherein the codings of the products prepared and tested are evaluated, the genomes either being sorted by ranking or divided into various evaluation categories, in accordance with a predetermined target function.
40. Process according to claim 39, wherein the target function may be any desired function construed from the combination of desired properties of the target compounds.
41. Process according to claim 38 or 40, wherein the evaluation criterion for the sorting or categorisation of the genomes is derived from the extent to which the individual products fulfil the target function.
42. Process according to any one of claims 39 to 41, wherein the biological activity, the physico-chemical properties and optionally further biologically relevant test results form the target function.
43. Process according to any one of claims 39 to 42, wherein

the concentration dependency of the test results is included in the target function.

44. Process according to any one of claims 40 to 43, wherein the properties are included in the target function with different and concentration-dependent weighting, the target function especially being a linear combination or polynome of those properties with "fuzzy" logic weightings.
45. Process according to any one of claims 40 to 44, wherein the "fuzzy" logic weightings of individual properties are dependent upon the extent to which other properties are fulfilled and upon the number of cycles already completed.
46. Process according to any one of the preceding claims, wherein the evaluated codings of the individual products are utilised to find a new set of optionally encoded starting materials, reaction conditions, modification and working-up procedures using a combinatorial optimisation procedure, such as, for example, a genetic algorithm or a pattern recognition process, a neuronal network or a combination of a genetic algorithm with a neuronal network, and to carry out corresponding MCRs.
47. Process according to any one of the preceding claims, wherein a reaction that has already been performed is not repeated.
48. Process according to claim 46 or 47, wherein the codings from the preceding cycle that are evaluated as being the best are used in the next cycle.
49. Process according to any one of claims 11 to 48, wherein

preferably a genetic algorithm or a pattern recognition process, such as a neuronal network or a combination of a genetic algorithm with a neuronal network, implicitly or explicitly correlates the occurrence of desired properties with the constituents of the coding of the corresponding product of the preceding cycles.

50. Process according to claim 49, wherein those constituents of the coding of the tested products which with greater probability correlate explicitly or implicitly with the desired properties are used with greater probability for the generation of new codings.
51. Process according to claim 49, wherein codings that have not received a good rating are not used for the generation of new codings.
52. Process according to claim 49 or 50, wherein individual constituents of the new codings are selected from the number of possible codings by means of a random generator.
53. Process according to claim 49, 50 or 52, wherein individual constituents of the new codings are removed from or added to the genome by means of a random generator.
54. Process according to claim 52 or 53, wherein the assignment of probability to a random selection of such a building block depends upon the type of that building block.
55. Process according to claim 52, 53 or 54, wherein the codings are divided randomly into one or more groups, so-called populations, the codings of a group especially

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being used only for the generation of new codings of a new group of genomes, each of those populations thus creating a new population.

56. Process according to claim 55, wherein after any desired number of cycles all populations of genomes are divided up into a new number of populations having the same number or a different number of genomes.
57. Process according to claim 56, wherein that new division is carried out when in a population a product has especially desirable properties.
58. Process according to any one of the preceding claims, wherein up to 30 cycles are required to find a product having especially desirable properties.
59. Process according to claim 58, wherein the probability of discovering such a product is estimated after as few as 2 to 6 cycles by means of the difference between the average extent to which the products of a population from a cycle x fulfil the target criteria and the average extent to which the products of a population from a later cycle $x+i$ fulfil the target criteria, where i is a whole natural number.
60. Process according to claim 59, wherein that difference can be used to select a new number of starting materials, reaction conditions, modifications or working-up procedures and to begin the iterative process afresh.
61. Process according to claim 60, wherein the iterative process is begun afresh when the difference is small.

62. Process according to any one of the preceding claims, wherein the chemical compounds contained in the reaction product that has exhibited the desired properties in the tests are purified and the structure thereof is determined.
63. Process according to any one of the preceding claims, wherein the analysis of the products is an investigation into whether the product has therapeutic properties.

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